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Proposed Registration Decision

Coniothyrium minitans **strain CON/M/91-08**

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Overview

Proposed Registration Decision for *Coniothyrium minitans* strain CON/M/91-08

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Contans WG Biological Fungicide and the end-use product Contans WG, containing the technical grade active ingredient *Coniothyrium minitans* strain CON/M/91-08 (*C. minitans* strain CON/M/91-08), to control fungal diseases in a variety of field and greenhouse vegetables.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Contans WG Biological Fungicide and Contans WG.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable¹ if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value² when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

¹ "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

² "Value" as defined by subsection 2(1) of the *Pest Control Products Act* "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on Contans WG Biological Fungicide and Contans WG, the PMRA will consider all comments received from the public in response to this consultation document.³ The PMRA will then publish a Registration Decision Document⁴ on *C. minitans* strain CON/M/91-08, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is *Coniothyrium minitans* strain CON/M/91-08?

C. minitans strain CON/M/91-08 is a microbial pest control agent used to control fungal plant disease on a variety of field and greenhouse vegetables. The end-use product Contans WG is a commercial fungicide product that contains *C. minitans* strain CON/M/91-08 as the active ingredient.

C. minitans strain CON/M/91-08 is a fungus that parasitizes *Sclerotinia sclerotiorum*. It specifically attacks long-lived, resting structures (sclerotia) of fungal plant pathogens belonging to the genus *Sclerotinia* in the soil.

Health Considerations

Can Approved Uses of *Coniothyrium minitans* strain CON/M/91-08 Affect Human Health?

***Coniothyrium minitans* strain CON/M/91-08 is unlikely to affect your health when Contans WG is used according to the label directions.**

People could be exposed to *C. minitans* strain CON/M/91-08 when handling and applying the product. When assessing health risks, several key factors are considered: the microorganism's biological properties (e.g. production of toxic byproducts), reports of any adverse incidents, its potential to cause disease or toxicity as determined in toxicological studies and the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

Toxicological studies in laboratory animals describe potential health effects from large doses to identify any potential pathogenicity, infectivity and toxicity concerns. When *C. minitans* strain CON/M/91-08 was tested on laboratory animals, there were no signs that it caused any significant toxicity or disease.

³ "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

⁴ "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Residues in Water and Food

Dietary risks from food and water are not of concern.

The *Food and Drugs Act* prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for the *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value determines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Strains of *C. minitans* are common in nature and the use of Contans WG in agricultural fields and in greenhouses to control fungal disease on vegetables is not expected to significantly increase natural environmental background levels of this microorganism. Furthermore, when *C. minitans* strain CON/M/91-08 was administered orally to rats no signs that it caused toxicity or disease were observed. Although certain strains of *C. minitans* produce secondary metabolites, *C. minitans* strain CON/M/91-08 is not known to produce any secondary metabolites and has demonstrated low toxicity in animal studies. The establishment of a MRL is not, therefore, required for *C. minitans* strain CON/M/91-08. As well, the likelihood of residues contaminating drinking water supplies is minimal to non-existent. Consequently, dietary exposure and risks are minimal to non-existent.

Occupational Risks From Handling Contans WG

Occupational risks are not of concern when Contans WG is used according to label directions, which include protective measures.

Workers using Contans WG can come into direct contact with *C. minitans* strain CON/M/91-08 on the skin, in the eyes, or by inhalation. For this reason, the label will specify that users exposed to Contans WG must wear gloves, long-sleeved shirts, long pants, a National Institute of Occupational Safety and Health (NIOSH) approved respirator (with any N, P, R or HE filter) and shoes plus socks.

For bystanders, exposure is expected to be much less than that of handlers and mixer/loaders and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Contans WG Is Introduced Into the Environment?

Environmental risks are not of concern.

Information on the environmental fate of *C. minitans* strain CON/M/91-08 suggests that, as a soil microorganism, it is likely that *C. minitans* strain CON/M/91-08 could survive in outdoor soil under suitable environmental conditions (i.e. the type of soil, moisture, acidity levels and temperature) but that over time the populations of *C. minitans* strain CON/M/91-08 should return to naturally occurring levels.

There are no published reports of disease associated with *C. minitans* in birds, wild mammals, fish, insects, earthworms, soil microorganisms and plants except for the intended pest and its close relatives, i.e. *Sclerotinia* species. Furthermore, studies designed to examine the effects of *C. minitans* strain CON/M/91-08 on fish, aquatic insects and algae reported no adverse effects. Although studies on birds, wild mammals, terrestrial insects, earthworms, soil microorganisms and terrestrial plants were not conducted, adequate information was available to determine that no risk to these non-target organisms are expected.

Value Considerations

What Is the Value of Contans WG?

Contans WG reduces *Sclerotinia* inoculum in the soil.

When applied to soil or crop residues, hyphae (threadlike structures) of *C. minitans* penetrate and subsequently degrade sclerotia. Infected sclerotia fail to germinate or produce apothecia, thereby preventing development of *Sclerotinia* disease.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Contans WG to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

• Human Health

Because of concerns with users developing allergic reactions through repeated high exposure to *C. minitans* strain CON/M/91-08, anyone handling or applying Contans WG must wear waterproof gloves, a long-sleeved shirt, long pants and shoes plus socks. In addition, mixers/loaders and applicators must wear a NIOSH approved respirator (with any N, P, R or HE filter).

• Environment

As a general precaution, label statements will be added to the label requiring handlers to not contaminate irrigation or drinking water or aquatic habitats. In addition, instructions will be provided to limit runoff from treated fields and to keep effluent from greenhouses containing this product from entering lakes, streams, ponds or other water bodies.

Next Steps

Before making a final registration decision on Contans WG Biological Fungicide and Contans WG, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

At the time the PMRA makes its registration decision, it will publish a Registration Decision on *C. minitans* strain CON/M/91-08 (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Coniothyrium minitans strain CON/M/91-08

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active microorganism	<i>Coniothyrium minitans</i> strain CON/M/91-08
Function	Control of sclerotia of <i>Sclerotinia sclerotiorum</i> and <i>S. minor</i> in agricultural soils
Binomial name	<i>Coniothyrium minitans</i> strain CON/M/91-08
Taxonomic designation	
Kingdom	Fungi
Phylum	Ascomycota
Class	Dothideomycetes / Coleomycete (anamorph stage)
Order	Pleosporales
Family	Anamorphic Leptosphaeriaceae
Genus	<i>coniothyrium</i>
Species	<i>minitans</i>
Strain	CON/M/91-08
Patent status information	Patents for <i>C. minitans</i> strain CON/M/91-08 as a biological control agent against <i>Sclerotinia sclerotiorum</i> and <i>S. minor</i> have been acquired in Germany and the United States. Patent applications have been filed in Europe and Canada.
Minimum purity of active	2×10^{10} colony forming units (CFU)/g
Identity of relevant impurities of toxicological, environmental and/or other significance	The technical grade active ingredient does not contain any impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product must meet microbiological contaminants release standards, and no mammalian toxins are known to be produced by <i>C. minitans</i> strain CON/M/91-08.

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Contans WG is manufactured as a continuous process product. The technical grade active ingredient exists only transiently and is not packaged. Therefore, physical and chemical properties for the technical grade active ingredient have not been determined.

End Use Product—Contans WG

Property	Results
Physical state	Wettable granule
Colour	Dark grey
Odour	Odourless
pH	7.3–7.6 in 7.5 pH tap water 6.5–6.6 in 6.6–6.7 pH CIPAC standard water D MT18
Persistent Foam	No persistence of foam (< 10 seconds)
Dispersibility	96.79–97.78%
Wet Sieve	10 g/100 mL solution left no residues on 0.075 mm sieve after 2–4 minutes
Wettability	2–3 seconds with or without stirring
Dust Content	<0.01%
Autoflammability	No autoignition at temperatures up to 400°C
Flammability	Non-flammable
Density	0.458 g/mL (uncompacted) 0.597 g/mL (compacted)

1.3 Directions for Use

Contans WG Fungicide is applied as a preplant soil-directed spray or as postharvest application to crop residues followed by soil incorporation using an appropriate cultivator. The application should be made at least three months prior to the typical onset of disease to allow the antagonistic fungus, *C. minitans*, to germinate, infect and degrade sclerotia. Contans may be used in a rotational cropping system and as a component of an integrated disease-management system.

1.4 Mode of Action

Coniothyrium minitans is generally considered to be a mycoparasite of sclerotia. The sclerotia of *Sclerotinia* species are covered by an epi-cortex which contains high levels of melanin in the outer cellular layers. Spores of *C. minitans* germinate in the presence of the host and enter the epi-cortex through small pores and lacerations to penetrate into the subcortex and medulla. Sclerotial cell walls consist mainly of glucans and chitin. *Coniothyrium minitans* secretes β -1,3-glucanase to degrade the sclerotia cell wall. Once inside the sclerotia cell, the infection progresses and asexual fruiting bodies (pycnidia) containing large amounts of conidiospores are produced from the metabolized substrates inside the parasitized sclerotia. The cytoplasm of the parasitized cells exhibit plasmolysis, aggregation and vacuolation often leading to lysis of the hyphae. As the number of vital sclerotia is reduced, the population of *C. minitans* also decreases. The vegetative organism disappears and the fungus rests as spores.

Under unfavourable conditions, *C. minitans* may not lead to rapid destruction of sclerotia, but can instead inhibit myceliogenic and carpogenic germination and thus decrease pathogenic infectivity.

In addition to parasitizing sclerotia, in vitro studies have indicated that the hyphae of *C. minitans* can directly interact with individual host hyphae. In these hyphal interactions, the hyphae of *C. minitans* grow alongside and penetrate the host hyphae. Penetration may occur via the formation of penetration pegs (appressorium) which pierce the walls of the host hyphae to cause indentation of the protoplasm and walls. After penetrating, the hyphae of *C. minitans* spreads within the host hyphae causing the parasitized mycelium to collapse and become necrotic. At late stages, pycnidia of *C. minitans* develop on the host mycelium. Under certain environmental conditions, hyphal interactions may be relevant in the field.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganism

The strain CON/M/91-08 is not substantially different from the classical description of the species: dark pycnidial wall; conidia size of $4.0\text{--}6.0 \times 3.5\text{--}4.0\text{ }\mu\text{m}$; three wall layers; vacuolated cytoplasm; and verrucose surface. Strain CON/M/91-08 can be further differentiated from other strains of *C. minitans* by random amplified polymorphic deoxyribonucleic acid analysis using DAF4, DAF6, DAF8 and DAF9 primers although this does not appear to be a routine component of the quality assurance program.

2.2 Methods for Establishment of Purity of Seed Stock

Lyophilized samples of pure stock cultures of *C. minitans* strain CON/M/91-08 are stored at -80°C and are used to prepare the inoculum for fermentation. *C. minitans* strain CON/M/91-08 is deposited in the German Collection of Microorganisms and Cell Cultures (DSMZ) under accession number DSM 9660.

Regular quality checks on the identity of *Coniothyrium minitans* are conducted during the production process. To ensure the purity and integrity of the lyophilized stock culture, the inoculum is cultured and examined microscopically for characteristic *C. minitans* colonies and contaminating microorganisms.

2.3 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products

The guarantee of the end-use product is based on both the total conidia count and the germination rate as follows:

$$\text{guarantee} = \text{minimum of } 1 \times 10^9 \text{ cfu/g} = \text{total conidia count} \times \text{germination rate}$$

The total spore count is determined by means of a counting chamber. The germination rate is determined by microscopic examination of culture plates for the development of germ tubes.

2.4 Methods to Determine and Quantify Residues (Viable or Non-viable) of the Active Microorganism and Relevant Metabolites

Methods to determine and quantify residues of *C. minitans* strain CON/M/91-08 are acceptable. Strains of *C. minitans* are common in nature and the use of Contans WG in agricultural fields and in greenhouses to control fungal plant disease on vegetables is not expected to significantly increase natural environmental background levels of this microorganism. Furthermore, when *C. minitans* strain CON/M/91-08 was administered orally to rats, no signs of toxicity or disease were observed.

Although certain strains of *C. minitans* produce secondary metabolites such as macrospheptide A, among others, *C. minitans* strain CON/M/91-08 is not known to do so. The mode of action associated with *C. minitans* strain CON/M/91-08 is directed at sclerotia of *Sclerotia* species and involves the use of lytic enzymes with no indication of antifungal metabolite activity. The results of supporting mammalian toxicity and pathogenicity studies did not indicate the presence of any metabolites of toxicological concern.

Based on the above information, the establishment of an MRL is not required for *C. minitans* strain CON/M/91-08 under section 4(d) of the *Food and Drugs Act* (adulteration of food) as defined under Division 15, section B.15.002 of the Food and Drugs Regulations.

2.5 Methods for Determination of Relevant Impurities in the Manufactured Material

The quality control procedures used to limit contaminating microorganisms during manufacture of Contans WG Biological Fungicide and Contans WG are acceptable. Regular quality checks on the identity of *C. minitans* are conducted during the production process by plating and by visual inspection to verify colony morphology and to detect any unusual colonies. The final product is also plated onto a number of selective media for detection of contaminating microorganisms. Batches showing any microbial growth on the selective media are discarded.

2.6 Methods to Show Absence of Any Human and Mammalian Pathogens

As noted in Section 2.5, several approaches are used to limit microbial contamination in Contans WG Biological Fungicide and Contans WG. These procedures include frequent purity checks to detect any unusual colonies and to verify colony morphology, as well as standard assays designed to detect contaminating fungi and total aerobes, yeasts and *Aspergillus* species, coliform bacteria, *Staphylococcus*, *Streptococcus* and *Salmonella*.

Acceptable microbial contaminant analysis data was submitted for five batches of Contans WG.

2.7 Methods to Determine the Storage Stability and Shelf-life of the Microorganism

The viability of *C. minitans* strain CON/M/91-08 in Contans WG was assessed by determining the guarantee (as described in Section 2.3 above) over a period of time and over a range of storage temperatures.

The submitted storage stability data supports the registrant's proposed storage period of one year at 4°C.

3.0 Impact on Human and Animal Health

3.1 Toxicity and Infectivity Summary

A survey of published literature revealed no cases of human infection from the species, *C. minitans*. *C. minitans* strain CON/M/91-08 is an indigenous soil-borne fungus that is a highly specialized mycoparasite that does not grow or multiply in the absence of host sclerotia. Naturally occurring spores of *C. minitans* can be found in the soil in the absence of sclerotia, but the spores remain inactive. Furthermore, infection by *C. minitans* strain CON/M/91-08 in animals is not possible as the microbial pest control agent (MPCA) does not grow at temperatures above 32°C.

A detailed review of the toxicological database for *C. minitans* strain CON/M/91-08 has been completed. The database for *C. minitans* strain CON/M/91-08 is complete (see Appendix I) consisting of laboratory animal (in vivo) toxicity studies (acute oral toxicity, acute pulmonary toxicity and infectivity, acute intraperitoneal injection infectivity, acute inhalation toxicity, acute dermal toxicity, and dermal irritation) currently required for health hazard-assessment purposes. These studies were carried out in accordance with currently accepted international testing protocols and good laboratory practices. As the end-use product is manufactured in a continuous process, there is no true technical grade active ingredient and therefore, it was considered acceptable that the acute oral toxicity study was performed with a suspension of the MPCA, referred to as CON/M/91-08. Also, as the end-use product formulation contains no formulants of toxicological concern, testing the end-use product, Contans WG, in the acute pulmonary toxicity/infectivity study was also considered acceptable. Although the dermal toxicity study and dermal irritation study should have been conducted with the end-use product, given that the end-use product formulation contains no formulants of toxicological concern, testing with a suspension of the MPCA was considered acceptable.

In addition to the required studies, a dermal sensitization study and an eye irritation study with *C. minitans* strain CON/M/91-08 were submitted. A bacterial reverse mutation assay and a cell culture assay conducted with Contans WG were also submitted. The scientific quality of the data is high and the database is considered sufficient to characterize the toxicity and infectivity of this pest control agent and product.

In an acute oral toxicity/pathogenicity study (limit test), there were no mortalities, no changes in body weight and no necropsy findings in Sprague Dawley Rats (5/sex) following oral gavage with CON/M/91-08 at 2000 or 2500 mg/kg body weight (bw). The 14-day oral LD₅₀ (rat) is >2500 mg/kg bw (males and females; limit test). CON/M/91-08 is of low toxicity in the rat when challenged via the oral route.

In an acute pulmonary toxicity and infectivity study, there were no mortalities, no changes in body-weight gain, and no treatment related-necropsy findings observed in fasted CD® rats

(35/sex) following intratracheal administration of 50 µL of Contans WG in 0.8% NaCl buffer (1g/2 mL) at 2.5×10^7 conidia/animal. Test substance was recovered in the caecum contents and in lung tissue but had completely cleared by Day Two and by Day Eight, respectively. The 21-day pulmonary LD₅₀ (rat) is $>2.5 \times 10^7$ conidia/animal (males and females). Contans WG is of low toxicity, and is not pathogenic in the rat when challenged via the intratracheal route.

In an acute intraperitoneal infectivity study (limit test), no mortalities and no significant toxicity were observed in Sprague Dawley Rats (5/sex) following intraperitoneal injection of undiluted CON/M/91-08 at 2000 mg/kg bw, equivalent to $\geq 1.6 \times 10^9$ conidia/animal. The 14-day intraperitoneal LD₅₀ (rat) is $>1.6 \times 10^9$ conidia/animal (males, females; limit test). CON/M/91-08 is not pathogenic to the rat by intraperitoneal injection. Clearance was not assessed.

In an acute dermal toxicity study (limit test), there were no mortalities, no local changes at the application site, no behavioural changes, and no gross necropsy findings observed in Sprague Dawley rats (5/sex/dose) following dermal exposure to CON/M/91-08 at 2000 or 2500 mg/kg bw for 24 hours. The 14-day dermal LD₅₀ (rat) is >2500 mg/kg bw (males and females; limit test). CON/M/91-08 is of low toxicity to the rat by the dermal route.

In an acute inhalation toxicity study, there were no mortalities, no intolerance reactions, no pathological findings upon necropsy, and no changes in body weight gain observed in Sprague Dawley rats (5/sex/dose) following nose-only inhalation exposure to an aqueous suspension of CON/M/91-08 at 6.04 or 12.74 mg per litre air for four hours. The 14-day inhalation LD₅₀ (rat) is >12.4 mg/L air (males and females; four-hour exposure). CON/M/91-08 is of low toxicity in the rat via the inhalation route.

In an acute irritation patch test, three Himalayan rabbits were dermally exposed to 0.5 mL of undiluted CON/M/91-08 for four hours and scored for irritation. No signs of dermal irritation were observed during the 72-hour observation period. CON/M/91-08 is non-irritating to the skin of rabbits.

In an eye irritation study on three Himalayan rabbits, 0.1 mL of undiluted CON/M/91-08 was instilled into the lower lid of one eye and scored for irritation. No corneal opacity, and no iridal or conjunctival irritation was observed over the 72-hour observation period. CON/M/91-08 is non-irritating to the eyes of rabbits.

The Guinea Pig Maximization Test of Magnusson and Kligman was used to assess the skin sensitization potential of CON/M/91-08 to guinea pigs. In the induction phase, ten young adult male guinea pigs were dosed with 0.1 mL of undiluted CON/M/91-08 by intracutaneous application to the shoulder region. As no irritation was observed by Day 6, the exposed skin was coated with 0.5 mL sodium lauryl sulfate in Vaseline to induce local irritation. On Day 7, a 2 mL topical dose was administered to the shoulder region for 48 hours to complete the induction phase. A positive control group dosed with potassium dichromate and a negative control group (water) were also included in the induction phase. Two weeks later a 2 mL challenge dose of undiluted CON/M/91-08 was applied topically to the flank region of test group and negative control group animals for 24 hours and examined for sensitization. The positive control dose

received a challenge dose of potassium dichromate. No mortalities occurred in any group and no signs of sensitization were observed following the challenge dose in the test group, nor in the negative control group. CON/M/91-08 showed no sensitizing properties by the test model of Magnusson and Kligman.

A bacterial reverse mutation assay with Contans WG suspended in water using bacterial mutants *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, TA 102, and TA 100 showed no mutagenic effect as indicated by the lack of increase in revertant colony numbers in a plate-incorporation assay (pre-experiment) at a range of ten concentrations between 0.316 and 5000 µg/plate, nor in a pre-incubation assay (main test) at a range of five concentrations between 10 and 5000 µg/plate, neither in the presence nor absence of metabolic activation. However, given that a plate test assay is inappropriate for testing microbial agents, the study was classified as unacceptable.

In a tissue culture study, an aqueous suspension of Contans WG (lysate; 4×10^9 conidia/mL) revealed no indication of mutagenic properties with respect to clastogenicity in human lymphocyte cells when tested at 312.5, 625, 1250, 2500, or 5000 µg/mL, either in the presence (four hour exposure) or absence (4 hour exposure, 24-hour exposure) of metabolic activation (S9 mix).

Higher tier subchronic and chronic toxicity studies were not required. This was because of the low acute toxicity of the MPCA, and lack of indications of infectivity, toxicity or pathogenicity in the test animals treated in the Tier I acute oral toxicity, pulmonary toxicity/infectivity, inhalation toxicity, intraperitoneal injection infectivity, and dermal toxicity tests.

Within the available scientific literature, there are no reports that suggest *C. minitans* has the potential to cause adverse effects on the endocrine system of animals. The submitted toxicity/infectivity studies in the rodent indicate that, following pulmonary and intraperitoneal injection routes of exposure, the immune system is still intact and able to process and clear the MPCA. Based on the weight of evidence of available data, no adverse effects to the endocrine or immune systems are anticipated for *C. minitans* strain CON/M/91-08.

3.2 Occupational /Bystander Exposure and Risk Assessment

3.2.1 Occupational

When handled according to the label instructions, the potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, and handlers exists, with the primary source of exposure to workers being dermal. Given unbroken skin is a natural barrier to microbial invasion of the human body, dermal absorption could occur only if the skin were cut, if the microbe were a pathogen equipped with mechanisms for entry through or infection of the skin, or if metabolites were produced that could be dermally absorbed. *Coniothyrium minitans* has not been identified as a dermal wound pathogen, and there is no indication that it could penetrate intact skin of healthy individuals. Also, infection in animals is unlikely given that the MPCA does not grow at temperatures above 32°C. Furthermore, growth of *C. minitans* strain CON/M/91-08 is host

specific, and CON/M/91-08 showed no toxicity and no irritation via the dermal exposure route. Toxicity testing with CON/M/91-08 also showed no signs of toxicity or infectivity via the oral, pulmonary, inhalation, or intraperitoneal injection routes of exposure.

The PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions, regardless of the outcome of sensitization testing. Label statements (i.e. Potential Sensitizer) and risk mitigation measures such as personal protective equipment, including gloves, long-sleeved shirts, long pants, NIOSH approved respirators (with any N-95, P-95, R-95 or HE filter), shoes and socks, are required to minimize exposure and protect handlers that are likely to be primarily exposed.

3.2.2 Bystander

Bystander exposures to the MPCA are not expected to pose an undue risk on the basis of the low toxicity/pathogenicity profile for *C. minitans* strain CON/M/91-08 and the assumption that precautionary label statements will be followed in the use of Contans WG.

The label does not allow applications outside of agricultural fields and greenhouses, therefore non-occupational dermal exposure and risk to adults, infants and children are low. Because the use sites are agricultural, exposure to infants and children in school, residential and daycare facilities is likely to be minimal to non-existent. Consequently, the health risk to infants and children is expected to be negligible.

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

Given that Contans WG is applied to and incorporated into soil either immediately before sowing or several months before planting, and that growth of *C. minitans* strain CON/M/91-08 is host specific, populations of *C. minitans* strain CON/M/91-08 are expected to be considerably reduced in soil at the time of planting, and therefore, colonization of the plant by the MPCA is unlikely to occur.

Furthermore, given that *C. minitans* is an indigenous soil microorganism it is unlikely that the use of Contans WG will result in an increase in residues on treated food/feed stuffs that is considerably higher than those found under natural conditions. Also, *C. minitans* strain CON/M/91-08 demonstrated no oral toxicity and no pathogenicity/infectivity via pulmonary or intraperitoneal exposure routes at the maximum dose tested in the Tier I acute toxicity/infectivity studies. Therefore, negligible to no risk is expected for the general population, including infants and children, or animals from residues in or on agricultural commodities.

C. minitans strain CON/M/91-08 is not known to produce any secondary metabolites and there have been no reports of adverse effects to humans from natural populations of *C. minitans*. Given that growth of the MPCA is host specific and the timing of application precludes direct exposure to edible commodities, the level of anticipated exposure to any potential secondary metabolites

produced by the MPCA is extremely low, and therefore, the risks from secondary metabolites to the general population, including infants and children, or animals are also negligible.

Higher tier subchronic and chronic dietary exposure studies were not required because of the low toxicity of the MPCA and lack of indications of infectivity, toxicity or pathogenicity in the test animals treated in the Tier I acute oral toxicity and acute pulmonary and intraperitoneal injection toxicity/infectivity studies. Therefore, there are no concerns for chronic risks posed by dietary exposure of the general population and sensitive subpopulations, such as infants and children.

3.3.2 Drinking Water

The likelihood that *C. minitans* strain CON/M/91-08 could enter neighbouring aquatic environments via spray drift or surface water runoff from field use or from greenhouse use of Contans WG is considered low. The potential transfer of *C. minitans* strain CON/M/91-08 to surface or ground water during runoff is considered minimal to non-existent in part due to the lack of mobility of *C. minitans* strain CON/M/91-08 as demonstrated in a soil column leaching study. Furthermore, there were no harmful effects observed in animals that were exposed orally in Tier I acute toxicity testing. In addition, *C. minitans* strain CON/M/91-08 does not grow or multiply in the absence of host sclerotia nor at normal mammalian body temperatures.

In addition, the label for Contans WG will instruct users not to contaminate drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes. Users are also requested not to allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters. Municipal treatment of drinking water will also likely remove the transfer of residues to drinking water. Therefore, potential exposure to *C. minitans* strain CON/M/91-08 in surface and drinking water is negligible, and consequently, no risks are expected from exposure to this microorganism in drinking water.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Calculations of acute reference doses and acceptable daily intakes are not usually possible for predicting acute and long-term effects of microbial agents in the general population or to potentially sensitive subpopulations, particularly infants and children. The single (maximum hazard) dose approach to testing MPCAs is sufficient for conducting a reasonable general assessment of risk if no significant adverse effects (i.e. no acute toxicity, infectivity or pathogenicity endpoints of concern) are noted in acute toxicity and infectivity tests. Based on all the available information and hazard data, the Agency concludes that *C. minitans* strain CON/M/91-08 is of low toxicity, is not pathogenic or infective to mammals, and that infants and children are likely to be no more sensitive to the MPCA than the general population. Thus there are no threshold effects of concern and, as a result, no need to require definitive (multiple dose) testing or apply uncertainty factors to account for intra- and interspecies variability, safety factors or margins of exposure. Further factoring in of consumption patterns among infants and children, special susceptibility in these subpopulations to the effects of the MPCA (including neurological effects from prenatal or postnatal exposures, and cumulative effects on infants and children of the MPCA and other registered micro-organisms that have a common mechanism of toxicity), does

not apply to this MPCA. As a result, the Agency has not used a margin of exposure (safety) approach to assess the risks of *C. minitans* strain CON/M/91-08 to human health.

3.4 Maximum Residue Limits

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established MRL. Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

As a product containing a naturally occurring soil fungus with growth that is restricted to a host, it is unlikely that the use of Contans WG will result in a significant increase in background levels of this organism. No adverse effects from dietary exposure have been attributed to natural populations of *C. minitans* and no adverse effects were observed in the acute oral toxicity study and there are no reports of known mammalian toxins for *C. minitans* strain CON/M/91-08.

C. minitans strain CON/M/91-08 is not known to produce any secondary metabolites and there have been no reports of adverse effects to humans from natural populations of *C. minitans*. Given that growth of the MPCA is host specific, and that timing of application precludes direct exposure to edible commodities, the level of anticipated exposure to any potential secondary metabolites produced by the MPCA is extremely low.

Therefore the establishment of an MRL is not required for *C. minitans* strain CON/M/91-08 under section 4(d) of the *Food and Drugs Act* (adulteration of food) as defined under Division 15, section B.15.002 of the Food and Drugs Regulations.

3.5 Aggregate Exposure

Based on the submitted toxicity and infectivity test data and other relevant information in the PMRA's files, there is reasonable certainty no harm will result from aggregate exposure of residues of *C. minitans* strain CON/M/91-08 to the general Canadian population, including infants and children, when the microbial pest control product is used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information. Given the product is to be used in agricultural fields and in greenhouses and is not allowed for use on turf, residential or recreational areas, dermal and inhalation exposure to the general public will be very low. Furthermore, there have been no adverse effects from exposure to natural populations of *C. minitans* in the environment. Even if there is an increase in exposure to this microorganism from the use of Contans WG there should not be any increase in potential human health risk.

3.6 Cumulative Effects

The PMRA has considered available information on the cumulative effects of such residues and other substances that have a common mechanism of toxicity. These considerations included the cumulative effects on infants and children of such residues and other substances with a common mechanism of toxicity. Besides naturally occurring strains of *C. minitans* in the environment, the Agency is not aware of any other microorganisms, or other substances that share a common mechanism of toxicity with this active ingredient. No cumulative effects are anticipated if the residues of *C. minitans* strain CON/M/91-08 interact with related strains of this microbial species.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental fate testing is intended to demonstrate whether an MPCA is capable of surviving or replicating in the environment to which it is applied, and could provide an indication of which non-target organisms may be exposed to the MPCA as well as provide an indication of the extent of exposure. Environmental fate data (Tier II/III) are not normally required at Tier I, and are only triggered if significant toxicological effects in non-target organisms are noted in Tier I testing.

Coniothyrium minitans is an indigenous soil microorganism that is often isolated from agricultural soil. The occurrence of *C. minitans* is closely related to the presence of its fungal host (usually *Sclerotinia sclerotiorum* and *S. trifoliorum*) and has, accordingly, been almost exclusively isolated from sclerotia. *Coniothyrium minitans* has been isolated in at least 29 countries, including Canada, and on all continents except South America where there were too few samples to rule out its presence. Strain CON/M/91-08 was isolated from a single pycnidium on a naturally infected sclerotium collected from oilseed rape near Malchow/Poel, Germany.

The natural density of *C. minitans* populations in soil is not available, however, it is likely influenced by environmental conditions as well as the availability of its fungal hosts. In nature, *C. minitans* appears to be closely associated with sclerotia of susceptible hosts. There are only a few reports of isolations directly from soil, but *C. minitans* has been shown to colonize slightly senescing plant tissue. The ability of *C. minitans* to survive in soil as mycelium, and sporulate on organic material other than sclerotia, is not known. In laboratory studies, *C. minitans* was not able to grow in non-sterile soil, indicating that it is a poor competitor. In soil, naturally occurring spores of *C. minitans* can persist ungerminated in disintegrated sclerotia for at least one year and the fungus can be recovered from soil in sclerotia for up to 18 months following application. However, *C. minitans* could not be recovered from sclerotia after 6 months when the soil temperature was greater than 25°C. Additional studies on agar media showed that spores of various isolates of *C. minitans* (including strain CON/M/91-08) could germinate and grow at temperatures up to 30°C, but no germination or growth was observed at temperatures of 33°C or above. Reduced germination rates were also observed in strain CON/M/91-08 following storage at -18°C. On malt extract agar, conidial germination, pycnidia development and hyphal extension occurred over a pH range of 3–8 with optimum values for all growth parameters being observed

between pH 4.5 and 5.6. Increasing the light period from continuous darkness to 12 hours light to 12 hours dark or continuous light, had no effect on conidial germination or hyphal extension, but the development of pycnidia was significantly increased.

With regard to the mobility of *C. minitans*, a soil column leaching study showed that vertical displacement of strain CON/M/91-08 does not occur in soil. In contrast, localized horizontal spread by water splash has been documented in published scientific literature. The dispersal of *C. minitans* in aerosol particles can be promoted by air movements, but this method of dispersal is considered of minor importance. There is also some evidence that soil organisms such as fungus gnats (Mycetophilidae), slugs, collembola, mites and sunflower maggots may contribute to its dispersal in soil. The isolation of *C. minitans* from aquatic environments has not been reported in public scientific literature.

4.2 Effects on Non-Target Species

4.2.1 Effects on Terrestrial Organisms

No studies were submitted to address the hazards of *C. minitans* strain CON/M/91-08 to terrestrial non-target organisms. Instead, scientific rationales were submitted to waive testing on birds, wild mammals, arthropods, non-arthropod invertebrates, soil microorganisms and plants.

Coniothyrium minitans is an indigenous soil fungus that is widely distributed on all continents but South America. As a result, many organisms are exposed to this microorganism as part of their natural environment. *Coniothyrium* species are found as either necrotrophic plant pathogens or saprotrophs living on decaying plant material. *Coniothyrium minitans* has been shown to colonize slightly senescing plant tissue, but it is considered to be a species which has lost its ability to infect plant material and is adapted to specifically attack sclerotia of *Sclerotinia* species in soil as a food source. No infection was reported after it was inoculated to 17 different terrestrial plant species that are known to be hosts for *S. sclerotiorum* and *S. minor*. These plant species included *Antirrhinum majus*, *Apium graveolens*, *Beta vulgaris*, *Brassica oleracea*, *Cheiranthus cheiri*, *Cichorium intybus*, *Coleus blumei*, *Cucumis sativus*, *Daucus carota*, *Helianthus annuus*, *Lactuca sativa*, *Lupinus regalis*, *Lycopersicon esculentum*, *Solanum melongena*, *Solanum tuberosum*, *Trifolium repens* and *Vicia fava*.

Minimal exposure is anticipated from its use in greenhouses, but non-target organisms dwelling in treated fields may be exposed to *C. minitans* strain CON/M/91-08 following application of Contans WG mainly by contact (soil organisms) and by the consumption of contaminated feed (insectivorous and earthworm-feeding animals as well as seed-feeding animals). However, exposure to foliage-dwelling arthropods and herbivorous organisms in the field are expected to be low because the use of the formulated product is limited to soil applications prior to sowing and the active translocation of *C. minitans* within the plant is not likely to occur.

Searches in various databases of published literature using the keyword "*Coniothyrium minitans*" found no reports of adverse effects to non-target terrestrial organisms. Rather, soil organisms such as insects and earthworms are considered to play a role in the dispersal of *C. minitans*. In

petri dish tests, the mite, *Acarus siro* L., and the collembolan, *Folsomia candida* Willem, were able to transmit the mycoparasite to uninfected sclerotia of *S. sclerotiorum*. Following feeding on *C. minitans*, fecal pellets of both species contained germinable inoculum of the mycoparasite, showing that the collembolans and mites clearly consumed the fungus. These conditions provided the fungus with an opportunity for an infection to occur, but no adverse effects on the animal species were observed. Furthermore, the survival of conidia or mycelia ingested via feed or direct colonization of birds and mammals is unlikely because no spore germination or mycelial growth was observed in *C. minitans* strain CON/M/91-08 at temperatures above 33°C. Acute mammalian toxicity and pathogenicity testing with *C. minitans* strain CON/M/91-08 produced minimal effects (see Section 3.1). *C. minitans* strain CON/M/91-08 was not toxic or pathogenic in the rat via the oral, pulmonary (intratracheal), inhalation, and intraperitoneal routes of exposure. No toxicity or irritation was observed in rabbits via dermal and ocular routes of exposure. Moreover, no harmful toxins are produced by strain CON/M/91-08.

The potential effect of *C. minitans* strain CON/M/91-08 to non-target soil microorganisms was qualitatively evaluated as part of soil column leaching study. In this study, *C. minitans* strain CON/M/91-08 was applied to the surface of soil columns at a rate of 5.0×10^8 conidia/m² (i.e. 5.0×10^{12} conidia/ha or 6.7×10^6 conidia/kg soil) and then sprinkled with 200 mm of a defined sprinkling water over a period of two days. The dehydrogenase activity and the qualitative content of aerobic bacteria and fungi in soil were evaluated following an incubation period of four weeks at 23.9–25.1°C. Neither the dehydrogenase activity of the soil microflora nor its composition appeared to be affected by the treatment compared to the untreated control. Furthermore, no reports of adverse effects to non-target soil microorganisms were found in published scientific literature. *Coniothyrium minitans* is a normal component of soil, and the organism is not expected to affect environmentally or economically important microbial species or microbiologically mediated biogeochemical processes.

Based on all the available data and information on the effects of *C. minitans* strain CON/M/91-08 to terrestrial organisms, there is reasonable certainty that no harm will be caused to birds, wild mammals, arthropods, non-arthropod invertebrates, plants or to other non-target microorganisms from the use of Contans WG.

4.2.2 Effects on Aquatic Organisms

Three toxicity studies were submitted to address the hazards of *C. minitans* strain CON/M/91-08 to aquatic non-target organisms. These studies included non-target freshwater fish, aquatic arthropods and freshwater algae.

In the acute freshwater fish study, no mortalities were reported after a single group of golden ide (*Leuciscus idus melanotus*, seven fish) was exposed to an aqueous limit concentration of 100 mg spore dry weight of *C. minitans* strain CON/M/91-08 per litre of dilution water (equivalent to approximately 1×10^8 spores/mL) over a period of 96 hours at $20 \pm 1^\circ\text{C}$ (16 hours light/8 hours dark) under static conditions. This study, however, deviated significantly from all standard microbial guidelines as well as the cited guideline, i.e. OECD 203. The duration of the study was too short, and the number of animals too low to properly evaluate the infectivity/pathogenicity

and toxicity potential of *C. minitans* strain CON/M/91-08 to freshwater fish. Furthermore, mortality as the only toxic endpoint is not as sensitive as inclusion of aberrant behaviour. These deficiencies did not invalidate the study results, but they did limit their usefulness in the risk assessment. Based on the results of this study, the 96-hour LC_{50} was determined to be greater than 100 mg spore dry weight of *C. minitans* strain CON/M/91-08 per litre of dilution water. A no observed effect concentration (NOEC) value could not be determined because no sublethal observations were made.

The toxicity of *C. minitans* strain CON/M/91-08 to *Daphnia magna* was studied under static conditions over a period of 48 hours. Daphnids (40/group) were exposed to *C. minitans* strain CON/M/91-08 at an aqueous limit concentration of 100 mg spore dry weight per litre of dilution water (equivalent to approximately 9×10^7 spores/mL) over a period of 48 hours at 19–20°C (16 hours light/8 hours dark) under static conditions. Another group (40 daphnids) remained untreated and served as a negative control. No mortalities were recorded during the study. As noted in the freshwater fish study, this study also deviated significantly from all standard microbial guidelines as well as some acute toxicity guidelines. The duration of the study was too short to properly evaluate the infectivity and pathogenicity potential of *C. minitans* strain CON/M/91-08 to aquatic arthropods, and mortality and immobility (as the only toxic endpoints) are not as sensitive as inclusion of aberrant behaviour and appearance. The study results were not invalidated by these deficiencies, although their usefulness in the risk assessment was limited. Based on the results of this study, the 48-hour LC_{50} was determined to be greater than 100 mg spore dry weight of *C. minitans* strain CON/M/91-08 per litre of dilution water. A NOEC value could not be determined because no sublethal observations were made.

The toxicity of *C. minitans* strain CON/M/91-08 to the freshwater green alga (*Scenedesmus subspicatus*) was studied at an aqueous limit concentration of 100 mg spore dry weight per litre of dilution water (equivalent to approximately 5.5×10^7 spores/mL) over a period of 72 hours at $25 \pm 1^\circ\text{C}$ (continuous lighting) under static conditions. An untreated group served as a negative control. The test and control suspensions were inoculated with approximately 10 times the normal algal concentration (i.e. $\sim 10^5$ algal cells/mL) in order to minimize the effects on the algal cell proliferation due to the pigmentation of the test material. No effects were noted on the growth of algae under the conditions of this study. Based on the results, the 72-hour EC_{50} and NOEC values were determined to be >100 mg/L and 100 mg/L, respectively. The duration of this study, however, was too short to properly evaluate the infectivity and pathogenicity potential of *C. minitans* strain CON/M/91-08 to freshwater algae.

No replacement studies were required despite the noted deficiencies in the study reports because exposure to non-target aquatic organisms are expected to be extremely limited based on the proposed use pattern, and *C. minitans* has no history of pathogenicity to any organism except the target *Sclerotinia* species. Minimal aquatic exposure is expected because *C. minitans* strain CON/M/91-08 will not be directly applied to water, and Contans WG will only be applied in greenhouses or will be incorporated into the soil following outdoor field applications.

A scientific rationale was also submitted to waive testing to non-target aquatic plants. The rationale stated that a comprehensive review on the biology of *C. minitans* reported no

pathogenicity from studies on 17 terrestrial host plant species that are known to be hosts of *Sclerotinia* species. Also, no reports of plant pathogenicity have been reported in published scientific literature. *Coniothyrium minitans* has been shown to colonize slightly senescing plant tissue. It is not; however, considered to be a pathogen of plants despite its relationship to other *Coniothyrium* species which are found as either necrotrophic plant pathogens or saprotrophs living on decaying plant material as well as species in the closely related genus, *Microsphaeropsis*. Moreover, minimal aquatic exposure is expected based on the proposed use of Contans WG.

Based on all the available data and information on the effects of *C. minitans* strain CON/M/91-08 to aquatic organisms, there is reasonable certainty that no harm will be caused to non-target aquatic organisms from the use of Contans WG. As a precaution, standard label statements will prohibit handlers from contaminating aquatic habitats, provide instructions on preventing runoff from treated fields and will prohibit effluent from greenhouses containing this product from entering lakes, streams, ponds or other water bodies.

5.0 Value

5.1 Effectiveness Against Pests

The efficacy data package submitted in support of the claims for suppression or control of *Sclerotinia* diseases in various crops consisted of 14 trials on winter canola, 8 trials on sunflower, 8 trials on field lettuce, 10 trials on beans, 1 trial on carrot, 3 trials on cabbage, 2 trials on celery and 4 trials on ornamental plants. In addition, trial results were provided to demonstrate compatibility of Contans WG with conventional fungicides.

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Field Uses

5.1.1.1.1 Suppression of *S. sclerotiorum* on Canola

A total of 14 trials on winter canola were submitted. The trials involved one pre-sowing (late summer/fall) application of Contans WG. Under high disease pressure conditions, 1 kg/ha Contans WG provided 90% control of the disease which was comparable to the commercial standard. In another trial, 2 kg/ha Contans WG resulted in 44% control of the disease. Under moderate disease pressure and compared to untreated controls, 1 and 2 kg/ha Contans WG both provided an average of 66% disease control. Under low disease pressure, 53–94% reduction in disease levels (average of 69%) was obtained. The performance of Contans WG was generally lower than the commercial standard. The data indicate good control of *Sclerotinia* disease in winter canola. However, due to some inconsistency in results under high disease pressure, the variability in level of disease control obtained under moderate disease pressure, and the higher control provided by the commercial standard, the claim for suppression, rather than control, of *S. sclerotiorum* on winter canola is supported.

No data specific to spring canola was provided. However, the results of the efficacy trials on winter canola are applicable because the pathogen is the same and the two crops belong to the same species. Additional support is provided by efficacy trials on sunflower because disease development and agronomic production practices are similar. The claim for suppression is extended to spring canola.

5.1.1.1.2 Suppression of *S. sclerotiorum* on Sunflower

A total of eight trials were submitted for review. Under low to moderate disease pressure, an average reduction of 53% (range: 40–74%) was provided by one application of Contans at 1 kg/row at seeding time. One application of Contans at 4 kg/ha, 1.5 months prior to transplanting of sunflowers, provided up to 92% control of the disease.

In monocropping studies on sunflowers, a solid formulation of Contans was applied once a year for three to four consecutive years. The solid formulation consisted of either bran or a mixture of barley, rye and sunflower seeds colonized by *C. minitans*. The incidence of Sclerotinia wilt decreased gradually from approximately 90% in the first year of application to 0% in the fourth year of the study. One and two years after the last treatment, *S. sclerotiorum* re-appeared and disease levels were 4% and 5 %, respectively. Two similar studies showed that Contans provided good control of the disease for three consecutive years. No commercial standards were included in these trials.

While disease levels were significantly different between plots treated with Contans and the untreated control, no commercial standards were used in the trials. In addition, the formulation used in these trials (solid formulation) is very different from the current formulation which makes (rate) extrapolation difficult. The claim for suppression of Sclerotinia wilt (*S. sclerotiorum*) of sunflower is supported based on limited efficacy data. Support for this claim is also based on extrapolation from the efficacy of Contans WG on canola and beans.

5.1.1.1.3 Suppression of *S. sclerotiorum* on Safflower

No trials were provided. However, the results from sunflower trials can be used to support the claim on safflower because these crops are attacked by the same pathogen and crop production practices are similar.

The claim for suppression of *S. sclerotiorum* (Sclerotinia head rot) on safflower is supported based on efficacy trials on sunflower.

5.1.1.1.4 Suppression of *S. sclerotiorum* on Dry Edible Beans

No data specific to dry edible beans were provided. However, this use can be supported based on efficacy data provided for field (snap) beans (Section 5.1.1.1.7). This is the same crop species but it is allowed to fully mature in the field and attain a specific seed moisture content before being harvested. The claim of suppression of *S. sclerotiorum* on dry edible beans is supported based on efficacy data provided for field (snap) beans.

5.1.1.1.5 Suppression of *S. sclerotiorum* on Soybean

No soybean trials were provided. However, support for this use can be extrapolated from field beans because disease development of Sclerotinia stem rot of soybean is similar to that of white mould of beans. The claim of suppression of *S. sclerotiorum* on soybeans is supported based on efficacy data provided for field beans.

5.1.1.1.6 Suppression of *S. sclerotiorum* and *S. minor* on Field Lettuce

A total of eight trials were submitted. Generally, there were significant differences between most of the Contans applications and the untreated control. Under low disease pressure, Contans applied at 4 kg/ha reduced head rot from 76–92% relative to untreated controls. The data indicated that *C. minitans* reduces Sclerotinia head rot in lettuce. However, most of the evidence presented consisted of disease reduction at low to moderate disease pressure. No trials with high disease pressure were submitted. Given Sclerotinia infection significantly affects product marketability and there is low tolerance for damage on lettuce, results from efficacy trials with low to moderate disease pressure support a claim for suppression.

5.1.1.1.7 Suppression of *S. sclerotiorum* on Snap Beans

A total of 10 field bean trials were submitted to support the claim for control of white mould on snap beans. At the proposed rate of 4 kg/ha, greater disease reduction was obtained when Contans was applied one month before planting than when applied at the time of seeding. Moderate control (38–78%) of the disease was obtained with Contans. The commercial standard provided significantly better disease control than Contans.

Although all trials submitted for review had low disease pressure, decreases in disease incidence were noted when Contans was used. In most trials, the differences between treatments were not significant but this may have been due to the low level of disease present in the plots. There was no significant difference when Contans was followed by a conventional fungicide that demonstrates no antagonism. The claim of suppression of *S. sclerotiorum* on bean is supported based on efficacy data.

5.1.1.1.8 Suppression of *S. sclerotiorum* on Carrot

One trial with low disease pressure conducted in the Netherlands was provided. This trial was not reviewed because the application rate is not known. However, disease development in carrots is similar to lettuce in that senescent foliage is attacked either by ascospores or by germinating sclerotia. In addition, production practices for carrots are similar to lettuce and celery, which are also attacked by *S. sclerotiorum*. The claim for suppression of *S. sclerotiorum* in carrots is supported based on field lettuce efficacy data.

5.1.1.1.9 Suppression of *S. sclerotiorum* on Cabbage

One trial with low disease pressure conducted in a greenhouse in Japan was provided. However, the results do not definitively support the claim because the rate used was two to four times higher than the proposed rate and no control treatment was included in the trial. The fungicide standard used for comparative purposes was not identified.

Two field trials from New Zealand with moderate disease pressure were submitted. A solid formulation of Contans applied at planting at a rate of 40 kg/ha significantly reduced Sclerotinia disease by an average of 53.5% compared to untreated controls. The rate used in this trial is lower than the proposed rate but it is expected that using a higher rate as stated in the proposed label will result in greater disease reduction. Carbendazim was used for comparative purposes, but this is not a commercial standard because it is not registered for this use in Canada. The claim for suppression of *S. sclerotiorum* in cabbage is supported based on efficacy data from field trials.

5.1.1.1.10 Suppression of *S. sclerotiorum* on Tomato

No field trials on tomato were submitted. A laboratory study on tomato stem pieces showed that *C. minitans* reduced the rate of tissue colonization by *S. sclerotiorum*. The disease on tomato is similar to the disease on bean. Therefore, the claim on tomato can be supported based on bean efficacy data. The claim for suppression of *S. sclerotiorum* on tomato is supported based on bean efficacy data.

5.1.1.1.11 Suppression of *S. sclerotiorum* on Celery

Two greenhouse trials were provided. In both trials, *C. minitans* grown in a mixture of maize meal and perlite was used. In the first trial, 4.3 L of *C. minitans* was applied per plot four days after sowing. The number of infected plants was reduced by 26% relative to untreated controls under moderate disease pressure. *C. minitans* did not perform as well as Ronilan (99% disease control). While Ronilan is used as a reference product in this trial, it is not registered for this use in Canada. Therefore it is not considered a commercial standard.

In another greenhouse trial, *C. minitans* in the solid formulation was applied at the rate of 0.6 L/m². The number of diseased celery plants was reduced by 6% relative to untreated controls under high disease pressure. No fungicide controls were included in the trial.

In these trials, *C. minitans* reduced disease levels marginally. However, evidence provided for lettuce may be used to support the claim on celery because Sclerotinia disease development in both crops is similar. The claim for suppression of *S. sclerotiorum* on celery is supported based on (field) lettuce efficacy data.

5.1.1.1.12 Suppression of *S. sclerotiorum* on Ornamental Plants Grown for Cut Flowers

The use of Contans on cut-flowers grown in the field is supported based on extrapolation from efficacy data for chrysanthemum and gerbera grown in plastic tunnels. However, only a claim for suppression rather than control can be supported for this use because the performance of Contans in the field is likely to be affected by various biological and environmental factors.

5.1.1.2 Greenhouse Uses

5.1.1.2.1 Control of *S. sclerotiorum* on Ornamental Plants Grown for Cut Flowers

Two trials each on gerbera and chrysanthemum grown in plastic tunnels in Poland were provided. In the 1998 and 1999 trials on gerbera, Contans provided 100% and 93% control, respectively, at the proposed rate (4 kg/ha) under high disease pressure. Rovral Flo 225 SC (active ingredient: iprodione) provided 69% and 71% control relative to untreated checks. In both trials the performance of Contans was significantly better than the commercial standard.

Under moderate and high disease pressure, Contans provided 92% and 89% control of Sclerotinia on chrysanthemums. Contans performed as well as or better than the reference product, Rovral Flo 225 SC. Rovral is registered for use on ornamentals in Canada to control *Botrytis* species and Rhizoctonia (damping-off) only. However, it is registered to control *S. sclerotiorum* in other crops such as canola, beans and lettuce. Therefore, it can be considered a commercial standard.

The following plants grown as cut-flowers that are susceptible to *S. sclerotiorum* may also be grown in soil in single-span greenhouse beds: snapdragon, salvia, dahlia, delphinium, larkspur, zinnia, lily, celosia and lisianthus. Given disease development in these crops is similar to chrysanthemums and gerbera, it can be expected that treatment of the soil with Contans will reduce Sclerotinia disease in these crops as well. The claim for control of *S. sclerotiorum* on cut flowers grown in soil in single-span greenhouse beds is supported based on efficacy data for chrysanthemum and gerbera.

5.1.2 Rate effect of *S. sclerotiorum* on Sclerotia

In greenhouse lettuce trials, *C. minitans* significantly reduced the mean number of sclerotia in soil (48%) and viability of sclerotia (31%) relative to untreated controls. In contrast, the viability of sclerotia did not differ between plots where Rovral was applied either once or every 2 weeks compared to those in the untreated control plots. Significantly more sclerotia (90% or over) were infected in plots treated with *C. minitans* than in control plots. For details, please refer to PMRA #1428944.

In a study on lettuce in Spain, evidence was provided indicating that the depth at which Contans is incorporated into the soil at the time of application impacts the product rate to be used.

The claim that 2–4 kg/ha is required for a depth of incorporation greater than 5 cm for winter canola, spring canola, sunflower, safflower, dry edible beans, and soybeans is supported.

The claim that 3–6 kg/ha is required for a depth of incorporation greater than 20 cm for lettuce, carrot, celery, cabbage and tomato is supported.

The claim that 6 kg/ha is required for a depth of incorporation greater than 10 cm for cut-flowers grown in single-span greenhouse soil beds is supported.

5.1.3 Overwintering Ability of Contans

Coniothyrium minitans has been isolated in Canada, indicating that it can overwinter here. In addition, monocropping trials on sunflowers conducted in Alberta and Manitoba demonstrated that under Canadian conditions Contans reduces Sclerotinia disease. A three-year field study involving beans in Lethbridge, Alberta also revealed that *C. minitans* survived Canadian prairie winters and resumed mycoparasitic activity on sclerotia of *S. sclerotiorum* the following spring when soil temperatures were above freezing.

5.1.4 Compatibility of Contans with Conventional Pesticides

Two sets of information were submitted to support the claim for the compatibility of Contans with conventional pesticides. A study by Budge and Whipps tested the effect of pesticides used in greenhouse lettuce. They demonstrated that radial growth and spore germination of three isolates *C. minitans* were inhibited by fungicides. The greatest sensitivity was toward iprodione and thiram. However, when *C. minitans* was exposed to two times the label rate for the various fungicides tested in soil-tray experiments, none of the test fungicides affected either the survival or their capacity to infect sclerotia. The number of colony forming units (CFU) remained constant over the four-week experimental period. The level of infection of sclerotia was always above 80% and was generally close to 95%. Sclerotial viability in *C. minitans* treatments was reduced to less than 20% compared to control treatments where sclerotial viability was always greater than 88%.

Iprodione, while very toxic to *C. minitans* in the in vitro tests, did not influence its survival or efficacy in the soil tray tests. The applicant attributes this difference in results to the moderating effect of the soil: pesticides are, in effect, diluted when applied to a higher volume of soil. In addition, many pesticides are quickly broken down in soil. It appears that the soil plays an important role in buffering the potentially toxic effects of pesticides on *C. minitans*.

The applicant performed tests on 37 fungicide products to determine their effect on *C. minitans*. These included in vitro (agar diffusion assay; radial growth, simulation of tank mixes) and in vivo tests (parasitism of sclerotia, viability test for extracted sclerotia). The tests confirmed that negative effects of conventional pesticides on *C. minitans* in in vitro tests do not necessarily result in negative effects in soil tray tests.

In greenhouse lettuce trials in the United Kingdom, the level of control by *C. minitans* was enhanced by the application of a single Rovral spray. The level of control obtained with this integrated treatment was statistically comparable to that obtained with the prophylactic spraying of Rovral. The ability of *C. minitans* to infect sclerotia was not inhibited by the Rovral spray, indicating that Rovral does not appear to have an adverse influence on *C. minitans*. This demonstrates that Contans has the potential to be used in an integrated disease management program for Sclerotinia disease.

5.1.5 Use of Contans in Cropping Systems with Frequent Crop Rotations or Short Intervals Between Crops

Results from crop rotation studies indicate that the efficacy of Contans is dependent on sufficient concentrations of *C. minitans* spores in the soil. Therefore, an application of Contans is necessary prior to planting each susceptible crop within the rotation. In addition, given development of Sclerotinia disease is highly dependent on climatic conditions that can be difficult to predict, preventative sprays must be applied. In the monocropping trial on sunflowers, disease levels gradually decreased to zero after yearly applications of Contans. Where short rotations are practiced, studies on greenhouse lettuce showed that the initial high population of *C. minitans* declines at the end of the crop cycle. Therefore, an application of Contans before the start of each susceptible crop is recommended.

The proposed label includes claims that "regular treatments of harvest residues at a rate of 0.5–2 kg/ha (for vegetable crops) or 0.5–1 kg/ha (for field crops) will reduce inoculum load in the soil". There are no trials that specifically addressed these claims. A rationale was provided by the applicant. Considering that *C. minitans* specifically attacks sclerotia of *Sclerotinia* species, a sound disease management strategy includes treatment of sclerotia on crop residues to help reduce disease levels in a succeeding susceptible crop.

The applicant indicated that in the first year that Contans is used, the goal is to eradicate as many of the older sclerotia in the soil as possible and prevent new ones from establishing on the residues. In subsequent applications to crop residues and prior to planting the crop, the main goal is to prevent the establishment of new sclerotia. Applications to crop residues can be done at a lower rate because the sclerotia are newly-formed and thus, more susceptible. They are also more directly exposed to *C. minitans* than older sclerotia present in the soil. Based on the mode of action of *C. minitans*, it is expected that repeated spraying of crop residues alone (even without incorporation) will eventually sanitize the field because the older sclerotia degrade after a few years and new ones will not be formed. Generally, the use of lower rates to keep the pest population low and biocontrol agent levels constant is an approach frequently used for biopesticides intended for use in a soil environment rather than as foliar treatments.

5.2 Economics

No market analysis was done for this submission.

5.3 Sustainability

Four active ingredients are currently registered for control of *Sclerotinia* diseases: azoxystrobin, boscalid, thiophanate-methyl, and vinclozolin. However, they are registered for only a few crops. For example, there are no products registered for the control of white mould on soybeans, celery or tomato. In some cases, an active ingredient may be registered for *Sclerotinia* control but its use is problematic because there is no tolerance or MRL established in other countries. The lack of established MRLs impacts exportation of these commodities to other countries.

There are a number of non-chemical strategies used to manage *Sclerotinia* diseases. These include crop rotations that reduce inoculum in the soil; weed control to remove alternate hosts of *Sclerotinia* species, water management and other strategies to decrease soil and canopy moisture, the use of disease free seed, as well as post harvest removal of plant debris that can serve as a source of *Sclerotinia* inoculum. Disease forecasting models and scouting techniques to optimize control strategies are also used.

Despite these strategies, control or suppression of *Sclerotinia* diseases can be difficult. The wide host range of *Sclerotinia* limits the effectiveness of crop rotations, and where control products are available, they do not affect the sclerotia in the soil. Sclerotia are the primary inoculum of the disease and cannot be eliminated with conventional products. Current chemical treatments are used after infection of plant parts have already occurred. Biological control agents normally present in the soil, such as *C. minitans*, are better suited to control plant pathogens that spend significant portions of their life cycle below the soil surface.

5.3.1 Survey of Alternatives

The alternative ingredients registered for control or suppression of diseases caused by *S. sclerotiorum* or *S. minor* is presented in Appendix I, Table 3.

There are no alternatives available for the following *Sclerotinia* diseases: head and stem rot on sunflower, stem rot on safflower, white mould on soybeans, soft rot on carrots, watery soft rot on celery, and stem rot on tomato.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Contans use can be compatible with current management practices. It can be applied to the soil prior to planting, or it can be applied to the crop residues after harvest. Pre-plant applications should be made as early as possible to allow *C. minitans* to germinate and attack sclerotia in the soil. The application made on crop residues is intended to reduce inoculum from infected plants. Incorporation of the soil layer sprayed with the spore suspension allows *C. minitans* to be in close proximity to the sclerotia present in the soil. An appropriate cultivator that growers already use in crop production, such as a rototiller, may be used.

Applications of Contans may also reduce Sclerotinia disease in a rotational cropping system. In a rotation involving Sclerotinia susceptible crops, applications are made either prior to planting the susceptible crop or to the crop residues after harvest. There is evidence to show that the use of Contans in successive years gradually reduces the amount of viable sclerotia.

Successful control of *Sclerotinia* with Contans depends on the ability of the grower to use the product in a way that allows a sustainable reduction of the inoculum in the soil. It is essential that the grower can use the product as a soil treatment at any time during the crop rotation cycle, i.e. not only prior to planting of a sensitive crop, but as part of a long-term suppression strategy.

Contans may also be used as a component of an integrated disease management system. Laboratory and soil tray tests showed that *C. minitans* is not affected negatively by certain conventional fungicides.

5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

No information is available regarding the risk of development of resistance in populations of *S. sclerotiorum* or *S. minor*. However, based on the mode of action of *C. minitans* and the supported use pattern for Contans WG Fungicide, the risk is considered to be low.

5.3.4 Contribution to Risk Reduction and Sustainability

Contans WG Fungicide is a microbial pest control product whose mode of action is infection and destruction of sclerotia of *Sclerotinia* species in soil. It is a non-chemical product intended to suppress or control Sclerotinia disease in various crops. Contans WG is considered a reduced-risk pesticide that has a low potential to harm the health of Canadians and the environment. Trials have shown that consecutive applications of Contans WG reduces disease levels in succeeding years, thereby reducing the need for foliar applications of chemical fungicides. Evidence was also provided showing that Contans WG was not inhibited by certain chemical fungicides in in vitro and soil tray experiments, indicating that it can be used as a component of an integrated disease management system.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy (TSMP), which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

In its review the PMRA took into account the federal TSMP and followed its Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of *C. minitans* strain CON/M/91-08 were also considered, including microcontaminants in the technical product, Contans WG Biological Fungicide, and formulants in the end-use product, Contans WG. The PMRA has reached the following conclusion.

- Contans WG Biological Fungicide does not meet the Track 1 criteria because the active ingredient is a biological organism and hence is not subject to the criteria used to define persistence, bioaccumulation and toxicity properties of chemical control products. There are also no formulants, contaminants or impurities present in the end-use product that would meet the TSMP Track 1 criteria. Therefore, the use of Contans WG Biological Fungicide and Contans WG is not expected to result in the entry of Track 1 substances into the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

Contans WG Biological Fungicide does not contain any contaminants of health or environmental concern identified in the *Canada Gazette* Part II, Volume 139, Number 24, pages 2641-2643: List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.

The end-use product, Contans WG, does not contain any contaminants of health or environmental concern identified in *Canada Gazette* Part II, Volume 139, Number 24, pages 2641-2643: List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.

7.0 Summary

7.1 Methods for Analysis of the Microorganism as Manufactured

The product characterization data for Contans WG Biological Fungicide and Contans WG, end-use product, were judged to be adequate to assess their potential human health and environmental risks. The technical material was fully characterized and the specifications were supported by the analyses of a sufficient number of batches. Storage stability data were sufficient to support a shelf life of six months at 4°C.

7.2 Human Health and Safety

The acute toxicity and infectivity studies submitted in support of *C. minitans* strain CON/M/91-08 were determined to be sufficiently complete to permit a decision on registration. *C. minitans* strain CON/M/91-08 was of low toxicity in the rat when administered via oral, pulmonary, dermal, and inhalation exposure and was not pathogenic or infective via the pulmonary and intraperitoneal injection exposure route. In the pulmonary injection infectivity studies, clearance was established by Day 8.

C. minitans strain CON/M/91-08 was not irritating to the skin and was not an ocular irritant. A bacterial reverse mutation assay with Contans WG was unacceptable given that a plate assay is inappropriate for testing genotoxicity of a microbial pest control agent. A lysate of Contans WG revealed no indications of mutagenic properties with respect to clastogenicity in a cell culture study with human lymphocyte cells.

Although *C. minitans* strain CON/M/91-08 showed no signs of dermal sensitization in the Guinea Pig Maximization Test of Magnusson and Kligman, the PMRA assumes that all microorganisms contain substances that can elicit positive hypersensitivity reactions, and exposure to allergens (including *C. minitans* strain CON/M/91-08) may cause allergies following repeated exposures.

When handled according to the label instructions, the potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, and handlers exists with the primary source of exposure to workers being dermal. Precautionary label statements on Contans WG and personal protective equipment will adequately mitigate the risks from exposure.

While *C. minitans* strain CON/M/91-08 has the potential to be a sensitizing agent, inhalation and dermal exposure are not a concern if the required dust/mist filtering respirator and appropriate personal protective equipment to be stipulated on the end-use product label is worn by applicators, mixer/loaders, and handlers. Furthermore, precautionary labelling will alert users of the potential dermal hazard of the end-use products.

The label does not allow applications to turf, residential or recreational areas. As the use sites are agricultural, exposure to infants and children in school, residential and daycare facilities is likely to be minimal to non-existent. Consequently, the health risk to infants and children is expected to be negligible.

Given the timing of application of Contans WG and that the growth of *C. minitans* strain CON/M/91-08 is host specific, and that *C. minitans* is an indigenous soil microorganism, it is unlikely that the use of Contans WG will result in an increase in residues on treated food or feed stuffs that is considerably higher than natural conditions. Also, *C. minitans* strain CON/M/91-08 demonstrated no oral toxicity and was not pathogenic or infective via pulmonary or intraperitoneal exposure routes at the maximum dose tested in the Tier I acute toxicity/infectivity studies. *C. minitans* strain CON/M/91-08 is not known to produce any secondary metabolites and there have been no reports of adverse effects to humans from natural populations of *C. minitans*. Therefore, negligible to no risk from residues in or on agricultural commodities is expected for the general population, including infants and children, or animals. Consequently, the establishment of an MRL is not required for *C. minitans* strain CON/M/91-08 under section 4(d) of the *Food and Drugs Act* (adulteration of food) as defined under Division 15, section B.15.002 of the Food and Drugs Regulations.

7.3 Environmental Risk

The non-target studies, scientific rationales and published scientific literature submitted in support of *C. minitans* strain CON/M/91-08 were determined to be sufficiently complete to permit a decision on registration.

Various data and information were submitted on the survival of *C. minitans* strain CON/M/91-08 in soil as well as its leaching potential in soil environments. These data and information showed that the MPCA is not likely to grow in soil or on plants in the absence of its host given it is a poor competitor; however, it may persist in soils for a significant period of time. The exact amount of time that it will persist in soil is likely to vary on many factors, including the type of soil, pH, humidity, the availability of sensitive hosts (i.e. sclerotia of *Sclerotinia* species) and temperature. Very little information, however, is known on the ability of *C. minitans* strain CON/M/91-08 to persist or grow in aquatic environments because its isolation from aquatic environments has never been reported in published scientific literature. The data and information also showed that *C. minitans* had limited potential to leach into the soil, but that there was some evidence that *C. minitans* could be dispersed by water splash and that some soil organisms may contribute to its dispersal in soil. No additional studies were required to address the environmental fate and behaviour of *C. minitans* strain CON/M/91-08. Environmental fate data (Tier II/III) are not normally required in the absence of significant toxicological effects in non-target organisms in Tier I testing.

Environmental effects studies and published literature were submitted to address the hazards of *C. minitans* strain CON/M/91-08 to non-target organisms. These studies and other published information showed that the use of Contans WG containing *C. minitans* strain CON/M/91-08 would not harm birds, mammals, arthropods (including honeybees), fish, non-arthropod invertebrates, plants, algae or soil microorganisms. Although the submitted aquatic toxicity studies did not entirely meet guideline criteria, no replacement studies were required because the exposure to non-target aquatic organisms is expected to be extremely limited based on the proposed use pattern. Also, *C. minitans* has no history of pathogenicity to any organism except the target *Sclerotinia* species.

As a precaution, standard label statements will prohibit handlers from contaminating aquatic habitats, provide instructions on preventing runoff from treated fields and prohibit effluent from greenhouses containing this product from entering lakes, streams, ponds or other water bodies.

7.4 Value

The value of Contans WG Fungicide lies in its ability to provide disease control by infecting sclerotia present in the soil. It has also been shown that the use of Contans in consecutive years reduces *Sclerotinia* disease significantly by preventing the formation of new inoculum.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of Contans WG Biological Fungicide and the end-use product Contans WG to control fungal diseases on a variety of field and greenhouse vegetables. An evaluation of current scientific data from the applicant, scientific reports and information from other regulatory agencies has resulted in the determination that, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

°C	degree(s) Celsius
µg	microgram
µL	microlitre
µm	micrometre
bw	body weight
CFU	colony forming unit
DACO	data code
EC ₅₀	effective concentration for 50% of the population
g	gram
g/cc	grams per cubic centimetre
kg	kilogram
L	litre
LC ₅₀	lethal concentration for 50% of the population
LD ₅₀	lethal dose 50%
mg	milligram
mL	millilitre
mm	millimetre
MPCA	microbial pest control agent
MRL	maximum residue limit
NIOSH	National Institute of Occupational Safety and Health
NOEC	no observed effect concentration
OECD	Organisation for Economic Co-operation and Development
PMRA	Pest Management Regulatory Agency
ppm	parts per million
TSMP	Toxic Substances Management Policy
WG	watersoluble granule

Appendix I Tables and Figures

Table 1 Toxicity and Infectivity of *Coniothyrium minitans* strain CON/M/91-08 and Its Associated End-use Products (Contans WG)

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference(s)
Acute Toxicity/Infectivity of <i>C. minitans</i> strain CON/M/91-08¹				
Acute Oral Toxicity	Rat - Sprague Dawley (CrI:CDRBR) Limit test: 5/sex/dose CON/M/91-08 at 2000 or 2500 mg/kg bw (potency not reported) No control groups	14-day 5 > 2500 mg/kg bw (males, females; limit test)	- No mortalities, no treatment related clinical signs, no necropsy findings, no changes in body weight gain. LOW TOXICITY	PMRA 1428832
Acute Pulmonary Toxicity and Infectivity ²	Rat - CD i. 35/sex dosed with 50 µL of Contans WG in 0.8% NaCl buffer at 2.51×10^7 conidia/animal ii. 5/sex vehicle control group treated with 0.8% NaCl buffer Sacrifices (5/sex/group) on Days 1, 2, 4, 8, 15, and 22	22-day LD ₅₀ $> 2.5 \times 10^7$ conidia/animal (males, females)	- No mortalities, no signs of toxicity, no changes in body weight gain - Marginal, non-specific inflammatory reactions consistent with intratracheal administration of a powder were noted - Test substance cleared from lungs by D8; cleared from contents by D2. LOW TOXICITY, NOT PATHOGENIC	PMRA 1428828
Intraperitoneal Injection Infectivity	Rat - Sprague Dawley Limit test: 5/sex administered CON/M/91-08 at 2000 mg/kg bw (1.6×10^9 conidia/animal)	14-day LD ₅₀ $> 1.6 \times 10^9$ conidia/animal (males, females; limit test)	- No mortalities, no significant toxicity, no changes in body weight gain, no necropsy findings - Clearance was not assessed. NOT PATHOGENIC	PMRA 1428831

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference(s)
Acute Dermal Toxicity ³	Rat - Sprague Dawley Limit test: 5/sex administered CON/M/91-08 at 2000 mg/kg bw (1.97-2.46 mL/kg bw) for 24 hours Results were confirmed by administering a second dose at 2500 mg/kg bw (5/sex) Control groups were not used.	14-day LD ₅₀ >2500 mg/kg bw (males, females; limit test)	- No mortalities, no changes in body weight gain, no necropsy findings - No local changes at the application site NON-IRRITATING	PMRA 1428830
Acute inhalation Toxicity	Rat - Sprague Dawley Rats (5/sex/dose) exposed to 6.04 or 12.74 mg of an aqueous suspension of CON/M/91-08/L air for 4 hours by inhalation (nose-only exposure chamber)	The 14-day LC ₅₀ >12.4 mg/L air (4 hour exposure)	Mass Median aerodynamic diameters: - low dose: 24.12 µm - high dose: 23.51 µm (cascade impact or determinations) - No intolerance reactions were observed - No mortalities. LOW TOXICITY	PMRA 1428827
Dermal Irritation ³	Rabbit - Himalayan Three animals dermally exposed to 0.5 mL of undiluted CON/M/91-08 for 4 hours	No calculations necessary.	- No signs of irritation during the 72-hour observation period. NON-IRRITATING	PMRA 1428829
Eye Irritation	Rabbit - Himalayan (3 animals) 0.1 mL undiluted CON/M/91-08 into the eye (unwashed) The untreated eye served as the negative control.	No calculations necessary	- No corneal opacity, no iridal, no conjunctival irritation over the 72-hour observation period. NON-IRRITATING	PMRA 1428826

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference(s)
Dermal Sensitization	Guinea Pig Maximization Test - Dunkin Hartley <u>Induction phase:</u> i. 10 animals dosed intracutaneously in the shoulder with 0.1 mL of CON/M/91-08 (5×10^8 conidia/mL). One week later, a second 2 mL topical dose was administered to the shoulder for 48 hours ii. Positive control (historical): 20 animals dosed with potassium dichromate iii. Negative control group: 5 animals dosed with water <u>Challenge phase:</u> Two weeks after topical induction dose i. 10 animals dosed topically in the flank with CON/M/91-08 with 2 mL for 24 hours ii. Positive control (historical): 20 animals dosed with potassium dichromate iii. Negative control group: 5 animals dosed topically in the flank with CON/M/91-08 with 2 mL for 24 hours	CON/M/91-08 showed no sensitizing properties under the test model of Magnusson and Kligman.	- No irritation by Day 6 therefore sodium lauryl sulfate in Vaseline (0.5 mL) was used to induce local irritation - No signs of sensitization were observed following the challenge dose in either the test group, or the negative control group - No changes in body weight gain - No mortalities NOT A SENSITIZER	PMRA 1428896

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference(s)
Genotoxicity - Bacterial Reverse Mutation Assay	Bacterial mutants were exposed to Contans WG Preliminary test: at 0.316, 1.0, 3.16, 10.0, 31.6, 100, 0316, 1000, 3160, and 5000 µg/plate with strain TA 100, in duplicate Main Assay: Test 1: Plate-incorporation at 0.316, 1.0, 3.16, 10.0, 31.6, 100, 0316, 1000, 3160, and 5000 µg/plate with strain TA 100, in duplicate Main Assay: Test 2: Pre-incubation (main test) at 100, 316, 1000, 3160, and 5000 µg/plate in duplicate Both tests were conducted in the presence and absence of metabolic activation.	The study is classified unacceptable as plate test assays are inappropriate for testing microbial agents.	- Mutant strains were <i>Salmonella typhimurium</i> strains TA 1535, TA 1537, TA 98, TA 102 and TA 100 - Potency of test substance confirmed to be 1.29×10^9 total spores/g (1.04×10^9 viable spores/g; 81.1% germination) - No cytotoxicity observed in the preliminary assay - No substantial increase in revertant colony numbers in any of the bacterial mutant strains tested in either main test, neither with, nor without activation.	PMRA 1428926

Study Type	Species, Strain, and Doses	Results	Significant Effects and Comments	Reference(s)
Tissue culture	Human peripheral lymphocyte cells <u>Treatment group:</u> Exposed to an aqueous suspension of a lysate of Contans WG (4×10^9 conidia/mL) at 312.5, 625, 1250, 2500 or 5000 µg/mL either: i) With metabolic activation (S9 mix) for 4 hours in duplicate ii) Without metabolic activation for 4 hours, or for 24 hours (single trial each level). <u>Negative control:</u> <i>aqua ad injectabilia</i> <u>Positive control:</u> i) With metabolic activation: cyclophosphamide ii) Without metabolic activation: mitomycin C	Contans WG showed no indication of mutagenic properties with respect to chromosomal or chromatid damage up to 5000 µg/mL.	- The mean incidence of chromosomal aberrations (excluding gaps) of cells treated with Contans WG in the presence (4 hour exposure), or absence of metabolic activation (4 hour, or 24 hour exposure) was within the normal range of the negative control group. - Positive control group induced significant chromosomal and/or chromatid damage.	PMRA 1428911

As the end-use product is manufactured in a continuous process, testing in the acute oral toxicity study with the a suspension of the MPCA, referred to as CON/M/91-08, was considered acceptable.

As the EP formulation contains no formulants of toxicological concern, testing the end-use product, Contans WG, in the acute pulmonary toxicity/infectivity study was considered acceptable.

Although the dermal toxicity study and dermal irritation study should have been conducted with the end-use product, given that the end-use product formulation contains no formulants of toxicological concern, testing with a suspension of the MPCA was considered acceptable.

Table 2 Toxicity to Non-Target Species

Organism	Exposure	Test Substance(s)	Significant Effects, Comments	Reference
Terrestrial Organisms				
Vertebrates				
Birds	Oral	A waiver was submitted based on the maximum growth temperature (33°C) of <i>C. minitans</i> which makes avian infectivity/pathogenicity unlikely. Minimal exposure is anticipated from its use in greenhouses, however, non-target organisms dwelling in treated fields may be exposed to <i>C. minitans</i> strain CON/M/91-08 following application of Contans WG mainly by contact (soil organisms) and by the consumption of contaminated feed (insects, earthworms and seed). <i>Coniothyrium minitans</i> has no history of pathogenicity to birds and searches in various databases of published scientific literature found no reports of adverse effects. Moreover, no harmful toxins are produced by strain CON/M/91-08. WAIVER ACCEPTED	1428972, 1428879	
	Pulmonary	Based on the waiver request for avian oral testing and on the lack of toxicity, pathogenicity and infectivity in the acute pulmonary toxicity/infectivity and intraperitoneal injection infectivity studies (Section 3.1), no additional data are required.		Not Required
Wild Mammals		A waiver was submitted based on the maximum growth temperature (33°C) of <i>C. minitans</i> which makes mammalian infectivity/pathogenicity unlikely. Minimal exposure is anticipated from its use in greenhouses, however, non-target organisms dwelling in treated fields may be exposed to <i>C. minitans</i> strain CON/M/91-08 following application of Contans WG mainly by contact (soil organisms) and by the consumption of contaminated feed (insects, earthworms and seed). <i>Coniothyrium minitans</i> has no history of pathogenicity to wild mammals and searches in various databases of published scientific literature found no reports of adverse effects. Furthermore, the laboratory animal studies on the rat and rabbit submitted in support of this registration and reviewed in Section 3.1 indicate that there is no pathogenicity and minimal toxicity from all routes of exposure at maximum hazard dose levels. Moreover, no harmful toxins are produced by strain CON/M/91-08. WAIVER ACCEPTED	1428972, 1428879	
Invertebrates				
Terrestrial Arthropods		Waivers were submitted based on the history of no pathogenicity to any organism except the sclerotia of <i>Scelrotinia</i> species. Searches in various databases of published scientific literature found no reports of adverse effects. Rather, there is some evidence that soil organisms, including fungus gnats (Mycetophilidae), slugs, collembola, mites and sunflower maggots may contribute to the dispersal of <i>C. minitans</i> in soil. WAIVERS ACCEPTED	1428972, 1428879	
Non-Arthropod species				1428879

Organism	Exposure	Test Substance(s)	Significant Effects, Comments	Reference
Soil Micro-organisms	A waiver was submitted based on the history of no pathogenicity to any organism except the sclerotia of <i>Scelrotinia</i> species Searches in various databases of published scientific literature found no reports of adverse effects. Furthermore, neither the activity of the soil microflora nor its composition was significantly affected after <i>C. minitans</i> strain CON/M/91-08 was applied to the surface of soil columns at a rate of 5.0×10^8 conidia/m ² (i.e. 5.0×10^{12} conidia/ha or 6.7×10^6 conidia/kg soil) and then sprinkled with 200 mm of sprinkling water over a period of two days (i.e. soil leaching study). The content of aerobic bacteria and fungi in soil was qualitatively evaluated following an incubation period of four weeks at 23.9–25.1°C. WAIVER ACCEPTED			1428972, 1428879, 1428920
Plants				
Terrestrial Plants	A waiver was submitted based on the history of no pathogenicity to any organism except the sclerotia of <i>Scelrotinia</i> species <i>Coniothyrium minitans</i> has been shown to colonize slightly senescing plant tissue, but it does not appear to be a plant pathogen despite its relationship to other <i>Coniothyrium</i> species which are found as either necrotrophic plant pathogens or saprotrophs living on decaying plant material. No infection was reported after <i>C. minitans</i> was inoculated to 17 different terrestrial plant species that are known to be hosts for <i>S. sclerotiorum</i> and <i>S. minor</i> . These species included <i>Antirrhinum majus</i> , <i>Apium graveolens</i> , <i>Beta vulgaris</i> , <i>Brassica oleracea</i> , <i>Cheiranthus cheiri</i> , <i>Cichorium intybus</i> , <i>Coleus blumei</i> , <i>Cucumis sativus</i> , <i>Daucus carota</i> , <i>Helianthus annuus</i> , <i>Lactuca sativa</i> , <i>Lupinus regalis</i> , <i>Lycopersicon esculentum</i> , <i>Solanum melongena</i> , <i>Solanum tuberosum</i> , <i>Trifolium repens</i> , and <i>Vicia fava</i> . WAIVER ACCEPTED			1428879

Organism	Exposure	Test Substance(s)	Significant Effects, Comments	Reference
Aquatic Organisms				
Vertebrates				
Freshwater fish (Golden ide; <i>Leuciscus idus melanotus</i>)	96-hour aqueous exposure (static)	7 fish/group i. Spore Isolate CON/M/91-08 containing spores of <i>C. minitans</i> strain CON/M/91-08 Nominal: 100 mg spore dry weight*/L Measured: 9.4×10^7– 1.0×10^8 spores/mL (Viability of spores was not assayed) ii. Dilution water (negative control) * This concentration was determined using a washed aliquot of test material, i.e. spore suspension. In the study, however, the original (unwashed) test material was applied.	None of the fish died during the course of the study. Infectivity was not assessed. 96-hour LC_{50} >100 mg spore dry weight/L (equivalent to approximately 1×10^8 spores/mL) A NOEC value could not be determined because no sublethal observations were made. Note: The study deviated significantly from all standard microbial guidelines as well as the cited guideline, i.e. OECD 203. Additional data are not required because aquatic exposure is expected to be minimal based on the proposed use pattern and <i>C. minitans</i> has no history of pathogenicity to any organism except the target <i>Sclerotinia</i> species. LOW TOXICITY	1428969

Organism	Exposure	Test Substance(s)	Significant Effects, Comments	Reference
Aquatic Arthropods (<i>Daphnia magna</i>)	48-hour aqueous exposure (static)	Range finding study: 10 daphnids/group i. Spore Isolate CON/M/91-08 containing spores of <i>C. minitans</i> strain CON/M/91-08 Nominal: 1 mL/L, 10 mL/L, 100 mL/L, undiluted Main study: 40 daphnids/group i. Spore Isolate CON/M/91-08 containing spores of <i>C. minitans</i> strain CON/M/91-08 Nominal: 100 mg spore dry weight*/L Measured: 9.0×10^7– 9.2×10^7 spores/mL (viability of spores was not assayed) ii. Dilution water (negative control) * This concentration was determined using a washed aliquot of test material, i.e. spore suspension. In the study, however, the original (unwashed) test material was applied.	Range-finding study: All of the daphnids in the undiluted test group were immobilized. The study author noted this observation was likely due to a depletion of oxygen in this test group. No other mortalities or immobilities were reported. Main study: No mortality or immobility was reported. Infectivity was not assessed. 48-hour $LC_{50} > 100$ mg spore dry weight/L A NOEC value could not be determined because no sublethal observations were made. Note: The study deviated significantly from all standard microbial guidelines as well as some toxicity guidelines. Additional data are not required because aquatic exposure is expected to be minimal based on the proposed use pattern and <i>C. minitans</i> has no history of pathogenicity to any organism except the target <i>Sclerotinia</i> species. LOW TOXICITY	1428968

Organism	Exposure	Test Substance(s)	Significant Effects, Comments	Reference
Plants				
Freshwater alga (<i>Scenedesmus subspicatus</i>)	72-hour aquatic exposure (static)	<u>Range finding study:</u> i. Spore Isolate CON/M/91-08 containing spores of <i>C. minitans</i> strain CON/M/91-08 Nominal: 1 mL/L, 10 mL/L, 100 mL/L, undiluted <u>Main study:</u> Initial algal concentration*: ~10⁵ algal cells/mL i. Spore Isolate CON/M/91-08 containing spores of <i>C. minitans</i> strain CON/M/91-08 Nominal: 100 mg spore dry weight**/L Measured: 5.5 × 10⁷–5.6 × 10⁷ spores/mL (Viability of spores was not assayed) ii. Dilution water (negative control) * Suspensions were inoculated with 10 times the normal algal concentration to minimize the effects on the algal proliferation due to the pigmentation of the test material. ** This concentration was determined using a washed aliquot of test material, i.e. spore suspension. In the study, however, the original (unwashed) test material was applied.	<u>Range-finding study:</u> This assay did not produce any useful results because the intensive colour of the test material inhibited the the growth of algae due to its ability to absorb/scatter light. <u>Main study:</u> After 72 hours, the control suspension proliferated by a factor of approximately 21 compared to a factor of approximately 19 for the test suspension. However, no detailed growth kinetics were performed. No morphological changes were noted in algal cell upon microscopic observation. Infectivity was not assessed. 72-hour EC₅₀ >100 mg spore dry weight/L 72-hour NOEC 100 mg spore dry weight/L Note: The study deviated significantly from all standard microbial guidelines. Additional data are not required because aquatic exposure is expected to be minimal based on the proposed use pattern and <i>C. minitans</i> has no history of pathogenicity to any organism except the target <i>Sclerotinia</i> species. LOW TOXICITY	1428970

Organism	Exposure	Test Substance(s)	Significant Effects, Comments	Reference
Aquatic plants other than algae	A waiver was submitted based on a comprehensive review on the biology of <i>C. minitans</i> which reported no pathogenicity from studies on 17 terrestrial host plant species that are known to be hosts of <i>Sclerotinia</i> species. No reports of plant pathogenicity have been reported in published scientific literature. <i>Coniothyrium minitans</i> has been shown to colonize slightly senescing plant tissue, but it does not appear to be a plant pathogen despite its relationship to other <i>Coniothyrium</i> species which are found as either necrotrophic plant pathogens or saprotrophs living on decaying plant material, as well as species in the closely related genus, <i>Microsphaeropsis</i> . Furthermore, minimal aquatic exposure is expected based on the proposed use of Contans WG. WAIVER ACCEPTED			1428972, 1428879

Table 3 Alternative Active Ingredients Registered for Disease Claims Supported On the Contans WG Biological Fungicide Label

Crop	Disease	Active Ingredient
Canola	White mould (<i>S sclerotiorum</i>)	Azoxystrobin; vinclozolin; boscalid
Beans	White mould (<i>S sclerotiorum</i>)	Vinclozolin, thiophanate-methyl
Lettuce	Lettuce drop, head rot (<i>S sclerotiorum</i> ; <i>S minor</i>)	Boscalid, <i>Bacillus subtilis</i> QST 713

References

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

1.0 The Active Ingredient, Its Properties and Uses

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2.0 Methods of Analysis

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B. ADDITIONAL INFORMATION CONSIDERED**1.0 Published Information****2.0 Methods of Analysis**

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3.0 Impact on Human and Animal Health**4.0 Impact on the Environment****5.0 Value****ii) List of Unpublished Information Considered****1.0 The Active Ingredient, Its Properties and Uses****2.0 Methods of Analysis****3.0 Impact on Human and Animal Health****4.0 Impact on the Environment****5.0 Value**